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Comprehensive multi-modality imaging approach in arrhythmogenic right ventricular cardiomyopathy (ARVC) – an EACVI expert consensus document

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Contents

Abbreviations

AC, arrhythmogenic cardiomyopathy

ARVC, arrhythmogenic right ventricular cardiomyopathy

CMR, cardiac magnetic resonance

ECG, electrocardiography

EF, ejection fraction

FAC, fractional area change

GLS, global longitudinal strain

LBBB, left bundle branch block

LGE, late gadolinium enhancement

LV, left ventricular

MDCT, multidetector computed tomography

PET, Positron emission tomography

PLAX, parasternal long axis view

PSAX, parasternal short axis view

PVC, premature ventricular complexes

SPECT, Single-photon emission computed tomography

RV, right ventricular

RVOT, right ventricular outflow tract

SCD, sudden cardiac death

SCMR, Society of cardiac magnetic resonance

STE, speckle tracking echocardiography

TFC, Task Force criteria

VT, ventricular tachycardia

1. Current knowledge

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy predisposing to ventricular arrhythmias, sudden cardiac death (SCD) and more rarely ventricular dysfunction and heart failure. Due to the frequent involvement of the left ventricle (LV) the term arrhythmogenic cardiomyopathy (AC) has recently been proposed to encompass both LV and RV disease and this expert consensus group acknowledges and recommends replacing ARVC with AC.

The 2010 Task Force Criteria (TFC 2010) have improved the sensitivity of AC diagnosis and combine data from different categories including imaging, electrical parameters from resting electrocardiogram (ECG) and Holter monitoring, family history, genetic testing, and tissue properties(1). Imaging modalities include angiocardiography, echocardiography and cardiac magnetic resonance (CMR), with qualitative assessment of RV wall motion abnormalities. In addition, a few quantitative measures are included in diagnosis with cut-off values for the RV outflow tract (RVOT) diameter and RV fractional area change (RV-FAC) by echocardiography and RV ejection fraction (RV-EF) by CMR.

Being a progressive cardiomyopathy, repeated cardiac imaging is needed in AC patients to follow disease progression and importantly, for risk assessment of life threatening ventricular arrhythmias. This expert consensus document will give clinical recommendations for how to use multi-modality imaging in the different aspects of AC disease, including diagnosis, follow -up, risk assessment and differential diagnosis.

2. Definition and Pathogenesis of AC

a. Anatomy and morphology

AC is a cardiomyopathy characterized by an acquired and progressive replacement of the ventricular myocardium by fibrous and fatty tissue (2, 3). The process starts from the epicardium or mid-myocardium and then extends to become transmural in the RV, leading to wall thinning and aneurysms, typically located at the inferior, apical and infundibular walls ("triangle of dysplasia"). The RV involvement can be either segmental or diffuse. The LV involvement is present in more than half of the cases, typically located in the subepicardium or mid-myocardium, and often confined to the postero-lateral region (2); a circumferential distribution is also observed. Hearts with isolated or predominantly LV involvement have been reported. The septum is affected in a minority of cases, typically on the right side. Fatty infiltration is not sufficient to achieve a clear-cut diagnosis and replacement-type fibrosis and myocyte degenerative changes are essential (4). Inflammatory cell infiltrates, together with myocyte injury, are often observed in the early stages of disease and during the process of evolution, mimicking myocarditis (2, 5, 6)

b. Pathogenesis, genetic background and inheritance.

Dysontogenetic (dysplasia), inflammatory (myocarditis), and degenerative (myocardial dystrophy) theories have been proposed as the mechanisms of AC(2). A familial background consistent with autosomal-dominant inheritance is present in most AC patients (7, 8). Recessive families with cardiocutaneous manifestations (palmoplantar keratoderma and woolly hair) have been reported and have provided the substrate for the initial recognition of disease causing genes (Naxos disease, Carvajal syndrome) (9, 10). Up to 50-60% of probands harbor a disease-causing gene mutation, leading to the current belief of a genetically-determined "cardiomyopathy".

Disease-causing genes mostly encode major components of the cardiac desmosomes and include plakoglobin, JUP; desmoplakin, DSP; plakophillin-2, PKP2; desmoglein-2, DSG2; and desmocollin-2, DSC2 (6). Compound/digenic heterozygosity was identified in up to 25% of AC-causing desmosomal gene mutation carriers, in part explaining the phenotypic variability. Non-desmosomal genes, including transforming growth factor beta-3, TGFβ3; desmin, DES; catenin-aT, CTNNA3; phospholamban, PLN; Lamin A/C, LMNA; titin, TTN have been reported, though the phenotypes often differ from classical AC(11).

How the mechanical and/or functional disruption of cell junctions by mutant desmosomal proteins leads to cardiomyocyte death and subsequent repair with fibrous and adipose tissue is under investigation. Abnormal cell-cell adhesion as well as intracellular signaling pathways (Wnt and Hippo/YAP) have been implicated in adipogenesis, fibrogenesis and apoptosis. Finally, gap junction and ion channel remodeling have also been demonstrated, suggesting that impaired mechanical coupling might account for abnormal electrical coupling (11, 12).

Key points:

- Arrhythmogenic cardiomyopathy is a progressive disease. Morphological changes start from the epi- or mid-myocardium and usually progress through all layers as a transmural myocardial disease
- The left ventricle is affected in >50% of cases and the term “arrhythmogenic cardiomyopathy” has been proposed to include biventricular disease
- A genetic mutation is found in up to 50-60% of probands, mostly affecting desmosomal genes
- Inheritance is most frequently autosomal dominant

3. Clinical characteristics

a. Symptoms and ECG

Family studies suggest that most individuals carrying potentially disease causing variants go undiagnosed(13). Data on clinical presentation will depend on the sources, ranging from the primary care physician to the coroner's pathologist. The classic clinical presentation is with exercise related ventricular tachycardia (VT) associated with awareness of rapid heartbeat, lightheadedness and/or syncope. Palpitation, when described, is of sudden onset and offset, rapid and different from the awareness of a 'heavy heart beat' typical of ventricular ectopic beats(5). Atypical chest pain which is precordial, but neither exertional nor relieved by rest, is reported in publications from referral centers, and may initially focus investigations on the exclusion of coronary artery disease. The mechanism is uncertain, but may relate to inflammation associated with a potential arrhythmic or hot phase of the condition.

The earliest disease manifestations are usually seen on the ECG, while the structural abnormalities which are best identified with imaging occur later in the natural history of the disease (14). Twelve lead ECG changes reflect myocardial areas of disease involvement. AC involving the RV free wall will typically manifest with inverted T waves in V1 to V3, and where there is LV involvement the T wave inversion may extend to lateral chest leads (V4-V6). T wave changes in inferior leads (II, III, aVF) often reflect RV infero-posterior wall involvement. Most patients present in sinus rhythm with a normal QRS axis, normal PR and QRS intervals, though a delayed upstroke of the S wave may be a subtle early disease manifestation, and is considered minor AC diagnostic criterion(1, 15). A normal ECG may occur in a mutation carrier, but in these individuals the risk of a life-threatening event as the initial clinical manifestation is very low. Similarly and importantly, a diagnosis based on imaging criteria with completely normal

ECG should be considered suspicious, and warrants careful review. AC with morphological changes limited to or predominately affecting the LV is increasingly recognized (6, 16-18). Such patients may have inferior and/or lateral T-wave inversion and ventricular arrhythmias with a configuration suggestive of a LV origin, often from the posterior lateral LV wall. In contrast, ventricular ectopy with left bundle branch block (LBBB) morphology, particularly with a superior axis, is typical of ARVC. LBBB morphology ectopy/ventricular arrhythmia with an inferior axis (R wave positive in leads II and III and negative in lead aVL) requires careful evaluation and differentiation from RVOT tachycardia, a condition which is not familial and rarely life-threatening. Ambulatory ECG monitoring during normal daily activity, ideally with 12 lead recordings, is an important diagnostic evaluation and often reveals ventricular arrhythmia in the absence of symptoms in affected individuals. The signal averaged ECG provides a marker of slow conduction and arrhythmic risk, but is neither a sensitive nor specific diagnostic test (19).

Key points:

- The classical clinical presentation is the occurrence of ventricular arrhythmias, typically with LBBB morphology and superior axis
- LBBB morphology ventricular arrhythmias with an inferior axis requires careful evaluation and differentiation from the more benign RVOT tachycardia
- ECG changes are often the first manifestation and a diagnosis based on imaging criteria with completely normal ECG should be considered suspicious

4. Structural remodeling in AC - RV/LV dominant types

Echocardiography and CMR are pivotal to detect structural and functional abnormalities in patients with suspected or genetically proven AC. Angiocardiography is also included in the TFC 2010, but it is an invasive procedure, now rarely performed. The importance of high sensitivity non-invasive tools for diagnosing early disease is emphasized by the fact that SCD may occur in individuals with no or subtle evidence of structural heart disease. Accordingly, it is

important to distinguish between individuals with **early, pre-symptomatic disease**, where no or minor and subtle structural changes can be detected in a single specific region of the RV (inflow tract, outflow tract, or apex, the "triangle of dysplasia") and symptomatic individuals with **advanced disease**, where severe RV involvement is evident, with or without LV involvement, typically affecting the posterior lateral wall. On the other hand, specificity is also important and in subjects with non-specific symptoms and/or subtle abnormalities, over-diagnosing, especially by non -experienced operators, must be avoided.

According to the TFC 2010 (1) the cardiac imaging diagnosis of AC is based on RV global or regional dysfunction and structural changes, with or without associated LV dysfunction (Table 1). Compared to previously published diagnostic criteria (20), TFC 2010 imaging criteria increased sensitivity to around 70%, keeping specificity high (around 95%). According to the TFC 2010(1), regional RV wall motion abnormalities are the main imaging criteria to diagnose AC, and the level of RV dilatation and RV global dysfunction determines whether or not a major or minor AC criterion is present. Despite the undisputed usefulness of the TFC 2010 criteria as a diagnostic tool for AC, concerns have been raised about its practical applicability as a screening tool. These include the complexity of the diagnostic workup, the necessity of memorizing several different imaging cut-off values both for major and minor criteria, the non-inclusion of RV inflow tract data and the low sensitivity of conventional echocardiographic criteria for the detection of subtle regional RV wall abnormalities in early disease stages (21).

a. Echocardiography

i. Conventional echocardiographic methods

Echocardiography is the first line imaging modality in AC, and the most commonly used imaging tool for follow-up of AC patients. Echocardiography is unexpensive, widely available and well tolerated. However, the echocardiographic diagnosis of AC is challenging and needs specific expertise. The echocardiographic protocol requires more views than those usually included in a routine study. Segmental evaluation of the RV is difficult due to the complex shape of the chamber and the position of the RVOT immediately under the sternum, narrowing the acoustic window for proximal structures. Moreover, the quantitative analysis of RV function is also difficult due to the complex RV anatomy and to its load dependency. A systematic qualitative assessment of RV function and dimensions should be performed initially, followed by quantitative measurements using conventional and advanced echocardiography (22, 23).

The typical morphological features in AC patients are RV dilatation, regional wall motion abnormalities or global RV dysfunction. The TFC 2010 (1) only includes only two-dimensional echocardiography as imaging criteria to diagnose AC: presence of RV akinesia, dyskinesia, or aneurysms together with measurements of RVOT diameter and RV FAC (Figure 1 and 2).

The RVOT diameter (1, 22, 23) can be measured from parasternal long axis (PLAX) (Figure 1) or from parasternal short axis (PSAX) views. When possible, the proximal RVOT diameter should be measured measured from PSAX. Measurements of RVOT diameter from PSAX are more robust and reproducible than from the long axis view (Figure 1B). Furthermore, the measurement of the ratio between the proximal RVOT and the aortic root diameter may be also assessed (24) with larger ratios indicating AC.

In addition, we recommend the routine and systematic assessment of RV inflow measurements in AC (Ref Leren JACC CVI in press)(RV basal diameter obtained from RV focused 4-chamber view, Figure 1C), as well as the inclusion of additional quantitative echo-strain data. (Table 2) The new parameters are reported in one or two studies (25-28) and are not validated in larger or multicenter studies. However, careful assessment of RV morphology and function will add to the accuracy of AC diagnosis.

ii. Advanced echocardiographic methods

New echocardiographic techniques may increase the performance of conventional echocardiography. Despite its intrinsic limitations, such as angle dependency and time consuming analysis, Doppler tissue imaging is useful in the assessment of RV longitudinal systolic function (peak velocity of the systolic (s') velocity of lateral tricuspid annulus in apical 4-chamber view, s') (Figure 3). RV function can be further assessed by speckle tracking echocardiography (STE), traced from the 4-chamber view with focus on the RV. RV peak systolic longitudinal strain values from six RV segments are averaged to calculate RV global longitudinal strain (RV GLS) (Figure 4). Alternatively, peak systolic strains from three RV free wall segments are averaged as a measure of RV free wall strain (29). Both RV GLS and RV free wall strain have been reported to be reduced in the early phases of AC (25-28). In addition to amplitude parameters, temporal parameters such as the time to peak strain (time from onset R on ECG to maximum RV longitudinal shortening by STE) should also be assessed. RV Mechanical dispersion may be calculated as the standard deviation of time to peak strain in a 6 RV segment model (26) (Figure 5) or in a 3 segments model (25) (Table 2).

iii. Three-dimensional echocardiography

Three-dimensional echocardiography (3DE) allows measurements of RV volumes overcoming the limitations of conventional 2D views with respect to orientation and reference points. RV and LV volume measurements will be of interest in patients with overt AC, while increased volumes are rare in early phases of AC. Three-dimensional echocardiography can obtain a reasonably accurate estimate of RV volumes and provide RV EF, but expertise is needed and practical recommendations regarding RV acquisition and analysis by 3DE have to be followed. Technical challenges include particularly patients with imperfect image quality or advanced AC patients with severely enlarged RV (Figures 6-10). Normal 3DE values of RV volumes are available (23, 30). However, no data currently exist for AC patients. Although 3DE tends to underestimate RV volumes, excellent correlations with CMR have been described (31). According to current guidelines, in laboratories with appropriate 3D platforms and experience, 3DE-derived RV EF should be considered as a method of quantifying RV systolic function. Roughly, an RV EF lower than 40- 45% usually reflects abnormal RV systolic function. (22, 23)

In summary, we recommend a broader approach of imaging methods than the current TFC, considering the inclusion of specific indications for imaging methods in probands (index patients, presenting with overt disease), follow- up of probands, and in family screening and in follow up of mutation positive family members (Chapter 7). Abnormal RV or LV function by other parameters will probably strengthen the suspicion of AC in unclear cases. In addition to parameters used in the TFC, we propose to evaluate additional parameters in patients with suspected or established AC. These parameters are not yet proven to increase diagnostic sensitivity but should be evaluated to prospectively gain new data in AC.

- Conventional echo parameters: TAPSE and RV basal diameter (REF Leren in press).

-Advanced echo parameters: RV GLS, LV GLS and mechanical dispersion by 2D-STE (26, 32), in family screening and follow up of mutation positive family members in which sensitive echocardiographic parameters are needed.

- Three-dimensional echocardiography parameters. However, the value of 3DE and cut off values for AC diagnosis and risk stratification need to be established.

Finally, new cut-off limits need to be considered and should be based on data from multiple large cohorts.

Key points:

- RV wall motion abnormalities in addition to quantitative measurements of RVOT diameter and RVFAC are the echo parameters included in the TFC 2010
- We recommend a broader, comprehensive and systematic assessment of RV geometry and function using both conventional and advanced echocardiographic techniques (Table 1)

b. CMR

CMR is less available and more expensive than echocardiography. However, in centres with adequate CMR equipment and expertise, the accuracy of CMR to detect subtle RV regional functional and structural wall abnormalities has been shown to be higher than conventional 2D echocardiography, due to the higher spatial resolution of the former(21). The tomographic, high-spatial resolution, non-invasive tissue characterization nature of CMR is particularly suited for the assessment of cardiomyopathies, including AC. CMR is erroneously considered the "gold standard" test to diagnose AC. As the TFC 2010 (1) emphasizes, the diagnosis of this disease is a composite of familiar, ECG, arrhythmic, histological, functional and structural features, in which CMR may play a role only to the latter two aspects. Great caution must be employed when the only abnormality in a presumed AC patient is found at the level of the RV on CMR, as it is

uncommon for AC patients to have a normal ECG and Holter monitoring but an abnormal CMR exam (33).

The CMR parameters from the TFC 2010 include RV regional dysfunction, reduced RV EF and enlarged indexed RV end-diastole volume, as well as localized RV wall thinning and aneurysmal formations (**Figure 11 and 12**). Despite the ability of CMR to detect myocardial fibro-fatty replacement in current routine clinical practice with the late gadolinium enhancement (LGE) and gradient echo with fat saturation technique, respectively, this aspect is not included in the TFC 2010 as a diagnostic criterion. In fact, at the time of compiling the 2010 TFC, fibro-fatty replacement by CMR was not considered a robust parameter that could be consistently reproduced in different laboratories. Moreover, the lack of a control population was considered a major drawback. With the improvement in imaging quality and the adoption of standard acquisition protocols, it remains to be seen whether fibro-fatty replacement by CMR will be considered in future reiterations of the TFC. CMR play also an important role in detecting AC phenocopies: unrecognized disease that could mimic AC such as cardiac displacement, RV volume overload, and myocardial scarring (identified in up to 4.6% of patients in a large cohort of 657 patients with suspected AC). (34)

Of note, the TFC 2010 lack specific diagnostic criteria for the non-classical variant of AC, which includes the dominant or isolated LV disease. This entity can be under-diagnosed and the abnormalities be attributed to other disorders, such as myocarditis, dilated or hypertrophic cardiomyopathy. CMR can identity LGE in a subepicardial/mid-wall distribution confined to the LV(18) .

Current CMR major criteria are shown in Table 1.

The value of CMR in children has also been recently reported and supported the good sensitivity of CMR in AC diagnosis. Furthermore, this study showed that fibro fatty replacement is rare in children with AC. (35)

Protocol in supplemental file

Key points:

- RV wall motion abnormalities in addition to RV volumes and RVEF are the CMR diagnostic criteria included in the TFC 2010.
- LGE on CMR is an important sign of disease and can be the only sign of LV involvement
- CMR alterations alone, without ECG and Holter abnormalities, are uncommon in AC disease except for the LV variant

c. CT

Cardiac CT is not included in the diagnostic algorithm and thus usually is not part of the initial screening of patients with suspected AC. Nevertheless, multidetector computed tomography (MDCT) has an excellent spatial resolution and allows accurate quantification of RV and LV volumes/function and, similar to CMR, detection of fatty tissue in the myocardium (ref 34). Currently, low radiation dose scan can be performed (1 to 2 mSv), while maintaining good temporal and spatial resolution (36).

According to the 2010 ACC/AHA appropriate use criteria (37), MDCT is appropriate for the evaluation of structural RV and/or LV remodeling in suspected AC, in particular for those patients with inadequate echocardiographic images and contraindications for CMR (36). Relevant MDCT parameters include RV dilatation, reduction of RV EF, severe segmental dilatation, and regional hypokinesis which are part of the major or minor criteria for the diagnosis of AC (1)(ref 33). In addition the visualization of epicardial and intramyocardial fat helps to assess

biventricular involvement. Thus MDCT can be helpful to differentiate between AC and other causes of ventricular arrhythmia (38) and could be used before epicardial ablation to localize both RV (39) and LV (40) fat related arrhythmic substrate.

CT protocol in supplemental file

d. Radionuclide angiography/SPECT/PET

Nuclear imaging is not included in the diagnostic algorithm of patients with suspected AC. Radionuclide angiography may provide measurements of RV volumes, RV ejection fraction and the standard deviation of regional times of end systole which can help to recognize diffuse or localized forms of AC (41) in patients with ventricular arrhythmias when the acoustic window is inadequate for echocardiography and the patient has contraindications to CMR(42).

Abnormal presynaptic myocardial sympathetic function, demonstrated using 123I-MIBG SPECT, is associated with a markedly higher risk of future recurrent life-threatening ventricular tachyarrhythmias both in patients with heart failure and in patients with AC (43, 44). These findings are associated with downregulation of LV myocardial b-adrenergic receptor density, demonstrated by 11C-CGP-12177 PET (45). Nuclear imaging of myocardial sympathetic function may therefore help for individualized risk stratification in AC independently from other common structural features.

Key points:

- MDCT is appropriate for the evaluation of structural remodeling in patients with suspected AC who have inadequate echocardiographic images and contraindications for CMR
- Nuclear imaging may be a potential risk stratification tool, but it still a research tool and needs further investigation

5. Role of imaging in early disease

a. Early signs

The overt stage of AC is preceded by a concealed stage with minor no or minor signs of disease. However, life-threatening arrhythmias can occur with only discrete myocardial structural changes (28, 46-49). On the other side, presence of structural abnormalities highly increases the risk of ventricular arrhythmias. Echocardiography is the first line imaging modality in AC. However, the diagnosis is more difficult at the early stage of the disease when only mild RV hypokinesia and dilatation are present (24, 47, 50). In this situation, additional information can be obtained from CMR, strain echocardiography (26, 51), and potentially from 3DE (52), although the latter two imaging techniques are not included in the current TFC 2010 since data are still either missing or limited. Teske et al. (28) focused on early detection of AC and found abnormal RV strain in 71% of asymptomatic carriers. A dilated RV basal diameter and pronounced RV mechanical dispersion may be other early echocardiographic signs of AC disease (Table 2). (25, 26, 53)

The role of CMR is important and it is the preferred imaging modality in the early diagnosis of AC, providing assessment of function and tissue characterization of both ventricles. Late gadolinium enhancement (LGE) is used to assess myocardial fibro-fatty replacement which may help to diagnose AC, although LGE is not specific for AC and may be present also in other cardiomyopathies (47). Table 3 reports the advantages and limitations of the imaging techniques.

Key points

- Advanced echo modalities and CMR are the preferred imaging techniques in the early diagnosis of AC, allowing to detect subtle changes in biventricular function and tissue characterization

6. Imaging in risk stratification of ventricular arrhythmias

Severely reduced RV function and LV involvement are important risk factors for ventricular arrhythmias in AC.(54) RV dilatation, reduced TAPSE and low FAC have been associated with arrhythmic risk in two studies (26, 50). Also right atrial dilation and tricuspid regurgitation have been related to arrhythmic events in one study on AC (50). Based on these and other findings, patients with abnormal RV function (Table 2) should be followed closely and be continuously evaluated for ICD implantation (48). The role of right chamber volume modifications for risk stratification of arrhythmias is controversial. In some cohorts RV EF and RV end-diastolic volume did not change significantly during long-term follow-up. (7, 55, 56) Importantly, involvement of LV function is a strong marker for risk of ventricular arrhythmias.

In comparison with echocardiography, CMR has the advantage of a better diagnostic accuracy of RV regional wall motion abnormalities, a characteristic with definite implications for risk stratification. A single study has indicated that an impairment of adrenergic innervation (obtainable by *123I-MIBG)* was associated with a higher incidence for future recurrences of VT in AC patients (44) as discussed above (Chapter 4d). This finding needs to be further investigated. To date, cardiac CT has not shown power in predicting VT in AC patients.

Table 4 summarizes advantages and disadvantages of the current imaging tools for risk stratification of VT in AC.

Key points

- Presence of any morphological or functional abnormalities in combination with electrical changes are the basis of AC diagnosis and indicate increased risk of ventricular arrhythmias.
- Risk stratification is commonly performed on an individual basis and definite evidence based parameters are lacking.

7. Imaging follow up in AC

Patients with AC and their family members should be followed clinically and undergo imaging testing on a regular basis, preferably at tertiary referral hospitals with specific experience in managing patients with AC(57). In order to maximize the sensitivity and specificity for correctly diagnosing AC it is essential that all diagnostic imaging options are used in a rational and comprehensive way, in order to establish

a) AC diagnosis

b) AC disease staging and progression

c) Risk assessment of ventricular arrhythmias

d) Assessment of heart failure and evaluation for cardiac transplant.

Among the different non-invasive cardiovascular imaging modalities, only echocardiography and CMR have been included in the TFC 2010(1). Other modalities with potential role in follow up of AC disease may be MDCT and 123I-MIBG SPECT as discussed above.

Imaging modality and follow up intervals differ between AC probands, family members and patients with ICD. In **probands** (index- cases of AC, presenting with overt disease), RV structural changes are usually present and the diagnosis is often made with echocardiography alone. CMR may also be performed at the initial diagnosis, if available, for a better morphologic and functional characterization, particularly if ICD is planned. CMR is mandatory in selected cases where the diagnosis depends on the presence or absence of imaging criteria and to assess the LV involvement by LGE CMR. However, probands have often experienced a life-threatening

ventricular arrhythmia and are often implanted with an ICD. Newer ICDs are CMR conditional (i.e. patients can be safely scanned following a specific protocol). During **follow- up,** echocardiography is repeated at regular intervals (Table 5) and CMR should be repeated if changes in clinical status and in questions not answered by echo. **Family screening** and follow - up of mutation positive family members, usually include individuals with no or only subtle morphological and functional findings. Because of the low sensitivity of echocardiography, both echo and CMR must be used to detect early phenotypes of the disease and repeated at regular time intervals (21, 57).

Importantly, there is no current evidence to guide the use of imaging during follow-up of patients with definite or possible diagnosis or in patients at-risk of AC. The following recommendations are based on cost-effectiveness considerations and consensus among members of the writing committee.

a. Patients with AC, implanted with ICD

AC patients implanted with ICD are often probands and imaging is used to establish AC diagnosis and to follow disease progression. These patients are normally followed with ICD checks every 6-12 months. Echocardiography should be performed to detect progressive LV heart failure and help evaluation for potential start of heart failure treatment. Furthermore, in AC patients with severe RV or biventricular failure, close echocardiographic follow -up may be needed for timing of heart transplantation. CMR is usually contraindicated (except in those with CMR conditional devices) and is not useful for clinical/management purposes if the diagnosis is already established.

b. Patients with definite diagnosis of AC and no ICD

In patients with a definite diagnosis of AC who are not implanted with an ICD, close follow- up is necessary. The potential need for ICD implantation must be discussed with the patient and considered at each visit. Careful evaluation of ECG, signal averaged ECG, Holter, CMR and echocardiographic changes are warranted. Patients must be informed to contact their referral centre if they experience palpitations, syncope or chest pain and these symptoms should lead to timely investigation and often ICD implantation. We propose at least yearly follow up visits including ECG and Holter and with a low threshold of new visits if the patient reports any new symptoms. Accordingly, echocardiography should be performed in all patients with definite diagnosis of AC who report changes in clinical status or in whom ECG changes are detected. These patients should be submitted to comprehensive echocardiography studies (including quantitative assessment of RV and LV size and function, RV outflow tract diameter, Table 2). Structural and functional changes in RV and LV are associated with higher risk of ventricular arrhythmias with higher risk along with more pronounced changes. It seems reasonable to repeat echocardiography every 2-3 years in clinically stable patients. For CMR measures, no cut- off values are established indicating when primary prophylaxis ICD implantation is indicated. Therefore the repeated use of CMR is currently not indicated. However, LGE LV involvement and progressive RV dysfunction indicate progression of disease and thereby higher risk of arrhythmias. CMR may therefore be appropriate to perform at first visit and to repeat every 5 years and on an individual basis. (57)

c. Mutation-positive family members, early diagnosis

The follow-up strategy for mutation positive family members of patients with AC or first degree relatives from families without identified mutations remains to be defined. Penetrance of

disease in family members is approximately 35% (58)and efforts should aim at identifying these individuals. ECG changes often precede overt morpho-functional abnormalities of the RV, and only small changes in conventional imaging parameters are expected during follow- up of family members. (59, 60). Importantly, the finding of morpho-functional abnormalities in family members should lead to close follow- up due to the increased risk of ventricular arrhythmias (48). However, tissue alterations, forming the substrate for ventricular arrhythmias, may be present although no wall motion abnormalities or RV dilatation are detected by conventional imaging parameters and technique. The tissue substrate may potentially be detected by LGE CMR and strain echocardiography(61). The delay in myocardial electrical activation and contraction inhomogeneity due to subtle tissue alterations could be detected by measuring RV mechanical dispersion by speckle tracking echocardiography (26, 62). We recommend CMR at baseline and for follow up at every 1-2 year in younger mutation positive family members either with borderline findings or without any symptom/sign of the disease. In asymptomatic mutation positive family members > 40 years of age, CMR could be repeated at longer intervals. Detection of CMR abnormalities during follow-up may further lead to closer follow up with ECG and Holter monitoring and evaluation of prophylactic ICD implantation. Follow up of family members should start from age 10, since events before this age are extremely rare.

Key points:

- Imaging follow up strategies differ between AC patients with and without ICD and in family members
- Imaging in AC patients with ICD should focus on disease progression in order to start heart failure treatment or initiate evaluation for transplantation
- AC patients with definite or possible diagnosis without ICD should be closely monitored due to high risk of arrhythmias. Worsening of imaging findings should tend to close arrhythmia monitoring or ICD implantation
- AC family members should undergo full non invasive testing at first visit and be followed with ECG and Holter. Imaging should be repeated if changes in clinical

status or ECG and be routinely repeated every 1-2 years in mutation carriers with borderline ARVC diagnosis and every 3-5 years in patients without any clinical, ECG or morphological findings.

8. Other diagnostic modalities in AC and shortcomings of TFC 2010

Updated diagnostic criteria were published in 2010 to improve sensitivity, but with the important prerequisite of maintaining diagnostic specificity. Quantitative imaging cut-off points to define a normal RV, to categorize the various degrees of morphofunctional abnormalities, for tissue characterization by endomyocardial biopsy, ECG, and signal-averaged ECG have been introduced. Genetic data have been also incorporated. However, although the TFC 2010 criteria acknowledge the existence of a broad disease spectrum, that includes also LV and biventricular subtypes, the revised criteria are addressing only the classical RV variant. No specific diagnostic guidelines do exist for the LV involvement, with the exception of: a moderate-to-severe LV dysfunction on imaging; lateral or inferolateral T-wave inversion (leads V_5, V_6, L_I, and aVL) and low voltage QRS complex on standard limb leads on ECG; and right bundle branch block/polymorphic ventricular arrhythmias.

CE- CMR is increasingly used to provide noninvasive tissue characterization of the RV myocardium but it is not included in diagnostic criteria due to the absence of proper control data. In addition to the identification of RV involvement, this technique can help to identify early or minor LV involvement, even in the absence of morphofunctional abnormalities detected by echocardiography (63).

Endomyocardial biopsy has been proposed for AC diagnosis in cases who remain undetermined after extensive non-invasive testing and in patients with suspected AC phenocopies. Transthoracic echocardiography is normally performed before biopsy to evaluate RV wall

thickness and preexisting pericardial effusions. After biopsy, transthoracic echocardiography (often with portable or pocket size echo devices) is useful in patients with sudden hemodynamic instability to assess the rare occurrence of haemopericardium and tamponade.

Electro anatomical mapping is another diagnostic tool used for diagnosis and to guide catheter ablation in AC patients with recurrent VT . This technique can be used to identify the abnormal low-voltage areas, which have been demonstrated to correspond to the loss of electrically active myocardium caused by fibro-fatty tissue, and is particular useful for differential diagnosis with idiopathic RV outflow tract tachycardia (64).

Finally, the new AC criteria include the identification of a pathogenic mutation categorized as associated or probably associated with AC in the patient under evaluation. However, it has been emphasized that a pathogenic mutation is a DNA alteration associated with AC that alters or is expected to alter the encoded protein, is unobserved or rare in a large non–AC control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree (so-called co-segregation). Strict adherence to these criteria is essential, particularly at present with the advent of next generation sequencing. Moreover, recent data are supporting the concept that "genetic load" is often making the difference in disease penetrance, since many patients have more than one pathogenic variant.

Key points:

- Genetic data, endomyocardial biopsy and electro anatomical mapping are additional diagnostic techniques helpful in the evaluation of AC

9. Imaging pre and post RF ablation

Imaging methods play an important role in facilitating and guiding radiofrequency ablation procedures of arrhythmias and detecting complications during or after the procedure. Performing radiofrequency ablation procedures may be technically challenging due to complex anatomy or variable geometry of the involved cardiac structures. Electroanatomical voltage maps can also be considered as an imaging technique, and is used for guiding RF ablation for VT. Recent advances in technology allow fusion of electroanatomical voltage maps with 3D morphological reconstructions from MDCT or CMR imaging to facilitate catheter manipulations. Identification of LGE by CMR correlates with foci of inducible ventricular tachyarrhythmia on electrophysiologic studies and may provide guidance for electroanatomic mapping and mode of ablation (e.g. endo- versus epicardial).(65) MDCT 3D-images, possibly integrated into 3D-EAM, are mainly helpful to evidence epicardial fat distribution, which correlates with low voltage and target ablation areas (clustering in the border of the fat region), and to avoid coronary arteries in the vicinity of target sites.(39)

Complications of radiofrequency ablation are rare but potentially life-threatening. Ventricular perforation and cardiac tamponade occur in approximately 1% of ventricular RF ablation procedures,(66) but its risk may be higher in AC, where the RV wall may be weakened by fibro-fatty replacement.(67) During or after ablation, transthoracic echocardiography (often with portable or pocket size echo devices or with intracardiac echo- when used for periprocedural monitoring) is useful in patients with sudden hemodynamic instability to assess haemopericardium/cardiac tamponade, thromboembolic events and acute ischemia from coronary artery lesions. Additionally, when an epicardial approach for VT ablation is used, ultrasound imaging may also be useful to detect iatrogenic lesions of abdominal organs or phrenic paralysis.

Key points:

- Pre ablation multi modality imaging with fusion of electroanatomical voltage maps with 3D morphological reconstructions from multi-slice CT or CMR facilitate catheter manipulations
- In patients with post ablation hemodynamic instability, echocardiographic examination should be performed to evaluate possible haemopericardium, thromboembolic events and acute ischemia

10. How to differentiate between AC from other arrhythmic diseases and acquired conditions:

a. RVOT-VT

The RVOT is the most common site of origin for idiopathic VT and frequent premature ventricular complexes (PVC) in patients with structurally normal hearts, known as RVOT-VT. In contrast to AC, RVOT-VT is usually a relatively benign condition, with generally well tolerated ventricular arrhythmias (5, 64). However, the RVOT area may also be origin of VT in patients with AC and in early stages of AC the distinction to RVOT-VT may be challenging. The treatment and prognosis differ substantially and an incorrect diagnosis may be devastating. Patients with RVOT-VT commonly have structurally normal ventricles, but frequent premature ventricular contractions (PVC) may cause myocardial remodeling with subsequent reduced function and dilatation, which further complicates the discrimination to AC. By cardiac imaging, fibro fatty replacement is not present in patients with RVOT-VT, while this is a hallmark of AC. Any findings of regional RV hypokinesia and dyskinesia by echo or CMR in addition to RVOT dilatation make the diagnosis of AC more probable and prognosis more severe (68).

Other diagnostic tests include family history, which is normally negative in RVOT-VT patients; genetic testing for AC related mutations, and Holter monitoring. ECG markers for AC

as T-wave inversions in the precordial leads are absent in RVOT-VT patients. High numbers of VPC (> 9000 per 24 hours) in the absence of severe structural alterations increase the probability that the diagnosis is RVOT-VT and not AC (25). In selected cases, electrovoltage anatomic mapping and endomyocardial biopsy can be determinant for differential diagnosis (64).

Key points.

- RVOT VT patients have more frequent PVC's than AC patients and usually no structural or mechanical alterations

b. Sarcoidosis and myocarditis

Patients with cardiac sarcoidosis or myocarditis have a few significantly different cardiac imaging characteristics when compared to patients with AC. The cardiac volume, in addition to the degree and location of cardiac involvement, can be used to distinguish between these disease entities. For instance, the presence of mediastinal lymphadenopathy, LV septal scar (LGE), significant LV dysfunction, and segmental areas of decreased uptake (201Thallium, 99-mTc Sestamibi, etc) in the ventricular myocardium that disappears or decrease in size during stress, and intense PET-FDG uptake in the myocardium should raise the suspicion for cardiac sarcoidosis(69). Consideration of cardiac sarcoidosis should be given if these imaging findings are observed during the evaluation for possible AC, particularly when conduction disturbances are also observed.

In myocarditis the LV is most often involved and the RV is rarely affected selectively. Areas of segmental perfusion defects coupled with FDG uptake, local oedema (T2 weighted images), epicardial/mid-wall LGE on CMR, and the presence of severe global or regional hypokinesia without a specific coronary territory distribution are in favour of myocarditis, when clinically suspected(70). Of note, although endomyocardial biopsy is still considered the gold

standard, it can be inconclusive since these diseases tend to be focal(71). Higher sensitivity is achieved through imaging guided endomyocardial biopsy (72, 73).

Key point.

- Sarcoidosis can mimic AC. PET-FDG should be performed and a positive test raise the suspicion for cardiac sarcoidosis
- Myocarditis may also mimic AC, and endomyocardial biopsy - although showing a low sensitivity - remains the gold standard for diagnosis

c. Dilated cardiomyopathies

Dilated cardiomyopathy may be particularly difficult to distinguish from non-classic (biventricular or left-dominant) forms of AC when there is early affection of the LV. Echocardiography has a limited role in this regard since LV dilation and/or systolic impairment are non-specific features. In many cases of left-dominant AC, LV structural abnormalities are localized in the posterolateral region (74, 75). CMR may further aid to diagnosis by providing tissue characterization and identification of intra-myocardial fat and fibrosis in addition to assessment of LV morphology and function. While findings like mid-wall LGE may be observed in both left dominant AC and dilated cardiomyopathy, the subepicardial distribution favors AC (76). Moreover, LV fatty infiltration was shown to be a prevalent finding in AC, often involving the subepicardial LV lateral wall and resulting in myocardial wall thinning (33, 77) .

Key points

- Left dominant AC can mimic dilated cardiomyopathy. Frequent arrhythmias and subepicardial fibro-fatty replacement on CMR favors AC diagnosis.

d. Congenital heart diseases

Congenital heart diseases with RV overload including anomalous venous drainage, ASD, are misdiagnosed as AC. ECG changes may help correct diagnosis in addition to careful imaging. Heart catheterization may be necessary to detect potential shunts.

e. Athlete's heart

RV and right atrium dilation are not specific to AC and is commonly found in athletes performing high-intensity exercise. Other important findings in athletes can be mild functional tricuspid regurgitation and dilation of the inferior vena cava (78) (79). These findings partly resemble echocardiographic findings in AC and can make it challenging to distinguish an athlete heart from AC by traditional cardiac imaging methods. Furthermore, athletic activity aggravates structural disease in AC patients which further complicate discrimination from athlete's heart (53, 80). RV cavity dilatation in athletes involves particularly RV inflow tract and is almost always associated with LV enlargement ("balanced enlargement")(79). Typical findings in AC, like RV thinning, bulging, and aneurysms will normally not be found in athletes. Importantly, TAPSE is typically normal and no convincing differences in strain measurements are found even in dilated RV in athletes (81, 82) (83). AC or another type of RV cardiomyopathy should be suspected if RV strain values or TAPSE suggest a decreased RV function. (26, 84) CMR must always be requested if the diagnosis of AC is suspected in athletes. However, CMR RV alterations alone, without abnormalities on ECG and Holter, are uncommon in AC disease.

Key points:

- AC is aggravated by athletic activity
- Abnormal measures of deformation imaging favor AC diagnosis

- CMR should be performed in unclear cases. CMR alterations alone, without abnormalities on ECG and Holter monitoring should favor athlete-induced changes and not AC diagnosis

f. Brugada syndrome

Although Brugada syndrome (BrS) is not associated with overt RV and LV structural abnormalities, endomyocardial biopsy, MDCT and CMR have identified mild RV abnormalities(85-89). In particular, RV wall motion abnormalities of the inferior wall have been detected by 2D echocardiography. A recent study has also shown in Brugada syndrome mild reduction of speckle tracking derived RV global longitudinal strain and of regional basal or mid RV free wall longitudinal strain which are, however, less pronounced than in AC (90, 91). Based on these findings, advanced cardiac imaging could be useful to distinguish Brugada syndrome from AC, in overlapping syndromes and when the clinical picture and ECG signs do not provide decisive elements for diagnosis.

Key points

- Overlap exists between AC and Brugada syndrome phenotypes including RV wall motion abnormalities. The clinical implication is unclear

11. Potential future role of different imaging modalities in AC

a. Echocardiography

Assessment of RV function by standard 2D echocardiography is limited to the RV lateral wall and important parts of the RV are not visible by 2D echo. The role of 3D echocardiography in AC is not explored. The multislice display of the RV 3D data set may allow a more comprehensive assessment of RV regional wall motion independent on the tomographic view and taking into account all RV walls (Figure 6-10) (92). In addition, 3D echocardiography should be

used in future studies to improve the assessment of the entire RV, including volumes and function.(23, 30, 31)

Strain imaging has a potential role in AC diagnosis and risk stratification for ventricular arrhythmias. By segmental analyses, regional dysfunction can be quantified and decreased strain values can confirm the visual impression of hypokinesia. Despite availability of normative values(29), issues about intervendor variability of strain values, reproducibility of regional strain and lack of standardization about the 2D view to be analyzed prevented absolute cut off values for segmental analyses to be established. Averaged RV strain from the 3 lateral RV segments may be a more robust measure of decreased function and previous studies have indicated that RV strain values worse than -25% may be markers of early disease and that values worse than -20% indicate severely reduced RV function(26, 53). Mechanical dispersion, reflecting dyssynchronous timing of contraction between different RV segments, may be used as an additional marker of early disease and interestingly also for arrhythmic risk stratification (26, 53).

Modalities using simulation techniques may further improve imaging in future, but are not in clinical use currently.

b. CMR

AC is a heterogeneous heart muscle disorder and genotype-phenotype correlations are demonstrating that the spectrum of the disease is possibly broader. Although traditionally considered as RV disease, there is increasing evidence of biventricular or even isolated LV forms. LV involvement is an increasingly recognised entity that can be missed by other imaging modalities, but it can be easily detected on CMR as LGE, even in patients without a definite diagnosis of AC according to the current TFC, which in fact does not take into account the LV

dominant form (93). The new high-resolution quantitative T1 mapping and inter- and intraventricular RV dyssynchrony might be novel promising markers for the early detection of the disease.

Key points

- Echocardiographic strain analysis assesses regional function and shows added information in AC, but RV assessment is limited to a few segments.
- 3DE will hopefully improve the assessment of RV regional wall motion, size and global function by echocardiography
- CMR T1 mapping may be a novel promising marker for early AC disease

c. PET/Nuclear

As the current findings point towards the role of adrenergic dysfunction in AC, the neural imaging methods may play more important role in the future (12). There are established methods for both conventional nuclear medicine as well as PET to image cardiac innervation but more clinical trials are warranted. As we learn more about the mechanisms of the disease, also specific molecular imaging probes focusing on disease process can be developed.

12.Summary

In this expert consensus document, we have provided an overview of currently available imaging modalities and parameters to be used in diagnosis and follow up of patients evaluated for AC. We propose a wider spectrum of echocardiographic parameters which can increase the sensitivity of the modality for AC. Furthermore, we have provided recommendations of imaging

use during follow up in AC patients and their family members. Finally, we have presented the most important differential diagnoses and how to distinguish these from AC.

Figure legends

Figure 1. Proximal RV outflow diameters (RVOT PLAX and PSAX) and RV basal diameter (RVD) (diastole). Courtesy of Dr J Saberniak

Figure 2. A. RV fractional area change (RVFAC) calculated from RV end diastolic area and B. from EV end systolic area as (RVEDA – RVESA/RVEDA) x 100) C. Left dominant type of AC with reduced LV function, LV dilatation, CMR showed epicardial fibrosis, ECG showed T inversion V1 – V6 and in inferior leads. The patients suffered from ventricular arrhythmia and was implanted with an ICD. Courtesy of Dr. J Saberniak

Figure 3. Reduced longitudinal function in a patient with AC (TAPSE < 17mm , s' tricuspid <9.5 cm/s)

Figure 4. Reduced RV GLS in an AC patient

Figure 5. Mechanical dispersion in AC. Compared to healthy volunteers, asymptomatic mutation carriers show increased TPSS-SD; compared to asymptomatic mutation carriers, overt dysfunction AC patients have high TPSS-SD (Sarvari et al, EHJ 2011)

Figure 6-9. 3D TTE images showing the potential of this technique to diagnose AC:

Figure 6. Subtricuspid valve aneurysm. Courtesy of Dr. D Muraru

Figure 7. Multiplanar display of the sub tricuspid aneurism. Left upper= 4CH, Right upper: 2CH; Left lower = long axis; Right lower= short axis at the level of the aneurysm (blue dotted line on longitudinal views). Courtesy of Dr. D Muraru

Figure 8. 12 slice display of the subtricuspidal aneurysm. Courtesy of Dr. D Muraru

Figure 9. Localized aneurysm. Left panel. RV focused apical 4CH view= normal; Central panel. Cropped longitudinal apical view showing the localized aneurysm (yellow arrow); Right panel. En-face view of the entry orifice of the aneurysm. Courtesy of Dr. D Muraru

Figure 10. Longitudinal (upper panels) and transversal (lower panels) cut planes showing the localized aneurysm (asterisk). Courtesy of Dr. D Muraru

Figure 11. CMR RVOT in and out view, cine image in end-diastole (A) and end-systole. Micro-aneurysms of the RVOT and RV diaphragmatic wall are present (white arrows).

Figure 12. CMR Four-chamber view, LGE image (A) and corresponding image in cine end-diastolic frame (B). The white arrow shows myocardial LGE (fibrosis) of the RV free wall.

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Table 1: Imaging criteria for AC from the Modified Task Force Criteria from 2010

Global or regional dysfunction and structural alterations
MAJOR
2D echo criteria
Regional RV akinesia, dyskinesia or aneurysm and 1 of the following measured at end diastole.
PLAX RVOT ≥32 mm
PSAX RVOT ≥36 mm
Fractional area change ≤33%
CMR criteria
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following
Ratio of RV end-diastolic volume to BSA ≥110 mL/m2 (male) or ≥100 mL/m2 (female)
RV ejection fraction ≤40%
RV angiography criteria
Regional RV akinesia, dyskinesia or aneurysm
MINOR
2D echo criteria
Regional RV akinesia or dyskinesia and 1 of the following measured at end diastole
PLAX RVOT ≥29 to<32 mm
PSAX RVOT ≥32 to<36
Fractional area change >33% to ≤40%
CMR criteria
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following
Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m2 (male) or ≥90 to <100 mL/m2

RV ejection fraction >40 to ≤45%

Diagnostic imaging criteria in AC modifyed from Marcus et al. AC: Arrhythmogenic cardiomyopathy, BSA: Body surface area, PLAX RVOT: parasternal long axis right ventricular outflow tract, PSAX RVOT: parasternal short axis right ventricular outflow tract, RV: Right ventricle.

Table 2. Quantitative standard and advanced echocardiographic parameters (with respective cut-off points) recommended in patients with suspected or ascertained AC. (* indicates the TFC 2010 parameters)

Parameter	Abnormal if
PLAX RVOT (mm) *	≥ 32
PLAX RVOT index (mm/m^2)*	≥ 19
PSAX RVOT (mm) *	≥ 36
PSAX RVOT index (mm^2) *	≥ 21
RV basal diameter (mm)	>41
RV fractional area change (%)*	≤ 33%
TAPSE (mm)	< 17
RV strain of lateral RV free wall (%)	worse than -20
RV mechanical dispersion (SD of Time to peak strain) (ms)	> 25-30 #
Three dimensional RV EF (%)	≤40
LV GLS (%)	worse than -18%

3 segments model and 6 segments model. EF: Ejection fraction, GLS: Global longitudinal strain, LV: left ventricular, PLAX RVOT: parasternal long axis right ventricular outflow tract, PSAX RVOT: parasternal short axis right ventricular outflow tract, RV: Right ventricle, TAPSE: Tricuspid annular plane systolic excursion.

Table 3: Advantages and limitations of imaging techniques

	Echocardiography	**CMR**	**CT**	**Nuclear**
Advantages	Large availability	Assessment of structure and function	If inadequate echocardiographic images and contraindications for CMR	For research purposes
	New techniques (strain)	Assess myocardial fibro-fatty replacement		
Limitations	Need of specific expertise	Need of specific expertise	Radiation Limited documentation	Limited documentation
	Complex anatomy of the RV	Complex anatomy of the RV	Complex anatomy of the RV	
	Load dependency of the RV	Load dependency of the RV	Load dependency of the RV	
	Quantitative evaluation difficult	Limited availability		
	Limited value at the early stage	Difficult at the early stage		
	Risk of under diagnosis	Risk of over diagnosis		

CMR: cardiac magnetic resonance, CT: computed tomography, RV: Right ventricle.

Table 4 Cardiac imaging tools for risk stratification of ventricular arrhythmias in AC

Imaging technique	Advantages	Disadvantages
2D Echocardiography	Low cost Large availability	Low reproducibility Suboptimal diagnostic accuracy Limited documentation
CMR	High reproducibility High diagnostic accuracy	High cost Suboptimal availability Limited documentation
1231-MIBG	Promising diagnostic accuracy	High cost Suboptimal availability Radiation exposure Limited documentation

CMR: cardiac magnetic resonance.

Table 5. Cardiovascular imaging follow-up in patients with definite arrhythmogenic right ventricular cardiomyopathy diagnosis and in family members (mutation positive or first degree relatives from families without identified mutations)

	Echocardiography	CMR	CT
AC patients with ICD	Clinically indicated	Not indicated or Contraindicated*	
AC patients without ICD	Clinical status and/or ECG changes or every 2-3 years	First visit Clinical status and/or ECG changes and patients are difficult to explore at echo	Patients who are difficult to assess with echo and unsuitable for CMR
Family members from approximately 10 years of age with borderline findings	Clinical status or ECG changes or 1-2 years in subjects < 40 years of age. Every 2 years in subjects > 40 years of age.	First visit Every 1-2 years in subjects < 40 years of age or when indicated** Every 3-5 years or when indicated in subjects > 40 years of age**	Patients who are difficult to assess with echo and unsuitable for CMR
Family members from approximately 10 years of age without any morphological findings	Clinical status or ECG changes or every 1-2 years in subjects < 40 years of age. Every 3-5 years in subjects > 40 years of age**	First visit Every 1-2 years in subjects < 40 years of age or when indicated** Every 3-5 years or when indicated in subjects > 40 years of	Patients who are difficult to assess with echo and unsuitable for CMR

		age**	

*except in patients with CMR compatible devices; ** clinical or ECG changes suggestive of disease progression; AC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; CT, multidetector computed tomography, ICD: implantable cardioverter defibrillator.